

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | |
|---|-----------|---|
| (51) International Patent Classification ⁶ : A61K 9/00 | A2 | (11) International Publication Number: WO 95/17165 (43) International Publication Date: 29 June 1995 (29.06.95) |
| (21) International Application Number: PCT/US94/14756 (22) International Filing Date: 21 December 1994 (21.12.94) (30) Priority Data: 08/172,451 23 December 1993 (23.12.93) US (71) Applicant: THE PROCTER & GAMBLE COMPANY [US/US]; One Procter & Gamble Plaza, Cincinnati, OH 45202 (US). (72) Inventors: MITRA, Sekhar; 7305 Demar Road, Cincinnati, OH 45243 (US). DECKNER, George, Endel; 10572 Tanager Hills Drive, Cincinnati, OH 45209 (US). (74) Agents: REED, T., David et al.; The Procter & Gamble Company, 5299 Spring Grove Avenue, Cincinnati, OH 45217 (US). | | (81) Designated States: CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>Without international search report and to be republished</i> <i>upon receipt of that report.</i> |
| (54) Title: TISSUE MOISTURIZING AND ANTIMICROBIAL COMPOSITIONS (57) Abstract The present invention relates to improved topical pharmaceutical compositions having improved aesthetics which are useful for imparting antimicrobial active. In particular, it relates to topical moisturizing compositions containing one or more antimicrobial active compounds. These compositions are also useful for providing relief from symptoms associated with, for example, vaginal yeast infections. | | |

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | |
|----|--------------------------|----|---------------------------------------|----|--------------------------|
| AT | Austria | GB | United Kingdom | MR | Mauritania |
| AU | Australia | GE | Georgia | MW | Malawi |
| BB | Barbados | GN | Guinea | NE | Niger |
| BE | Belgium | GR | Greece | NL | Netherlands |
| BF | Burkina Faso | HU | Hungary | NO | Norway |
| BG | Bulgaria | IE | Ireland | NZ | New Zealand |
| BJ | Benin | IT | Italy | PL | Poland |
| BR | Brazil | JP | Japan | PT | Portugal |
| BY | Belarus | KE | Kenya | RO | Romania |
| CA | Canada | KG | Kyrgyzstan | RU | Russian Federation |
| CF | Central African Republic | KP | Democratic People's Republic of Korea | SD | Sudan |
| CG | Congo | KR | Republic of Korea | SE | Sweden |
| CH | Switzerland | KZ | Kazakhstan | SI | Slovenia |
| CI | Côte d'Ivoire | LI | Liechtenstein | SK | Slovakia |
| CM | Cameroon | LU | Luxembourg | SN | Senegal |
| CN | China | LV | Latvia | TD | Chad |
| CS | Czechoslovakia | MC | Monaco | TG | Togo |
| CZ | Czech Republic | MD | Republic of Moldova | TJ | Tajikistan |
| DE | Germany | MG | Madagascar | TT | Trinidad and Tobago |
| DK | Denmark | ML | Mali | UA | Ukraine |
| ES | Spain | MN | Mongolia | US | United States of America |
| FI | Finland | | | UZ | Uzbekistan |
| FR | France | | | VN | Viet Nam |
| GA | Gabon | | | | |

TISSUE MOISTURIZING AND ANTIMICROBIAL COMPOSITIONS

TECHNICAL FIELD

5 The present invention relates to improved topical pharmaceutical compositions having improved aesthetics which are useful for imparting antimicrobial actives. In particular, it relates to topical moisturizing compositions containing one or more antimicrobial active compounds. These compositions are also useful for providing relief from symptoms associated with, for example, vaginal yeast infections.

BACKGROUND OF THE INVENTION

10 Several environmental and pathologic conditions produce drying or desiccation of membranous tissue of the mammalian body. These conditions produce dry mouth (xerostomia), dry eye (sicca conditions) and dry vaginal, dry nasal or dry rectal mucosa, and/or dry skin that are aesthetically displeasing and/or irritating to the individuals having such conditions.

15 One method for moisturization of dry tissue uses an oily substance as the principal ingredient in the form of creams, lotions, or salves that are applied to the affected tissue in an attempt to prevent further dehydration of the tissue. They act by placing a water-impermeable hydrophobic barrier over the treated tissue. Petrolatum, mineral oil, lanolin and isopropyl myristate are examples of hydrophobic materials so used. These preparations alone provide only symptomatic relief. In addition, they impart a greasy, sticky feel to the skin and stain clothing.

20 Another method for moisturization uses hydrophilic molecules which can attract water. Hydrophilic small molecules such as glycerin and glycerin/water mixtures, urea, and propylene glycol are known humectants said to be useful in moisturizing skin.

25 Several synthetic hydrophilic materials, which in the presence of water adhere to the skin and/or mucous membranes, have been used by themselves or in conjunction with one or more active or treating agents in various pathological conditions, but they have not been used in moisturizing compositions having a specific viscosity range, for dryness of epithelial cells such as those of the skin or mucosa. These hydrophilic materials are often referred to in the art as hydrogels.

30 Disorders in these mucosal areas can often lead to infections, such as a yeast infection. Yeast infections are among the most common to mankind. Microbes of the genus *Candida* are normal inhabitants of the bowel. These microbes are also found on the skin and in sputum of healthy individuals. *Candida albicans* is by far the most pathogenic member of the *Candida* family. Suitable treatments for such infec-

tions are well known. For example, U.S. Patent No. 4,226,848 discloses a composition for adhering a pharmaceutical preparation to the mucosa of the oral or nasal cavities. An exemplary acrylic acid polymer disclosed therein is the lightly cross-linked acrylic acid-allyl sucrose copolymer available under the trademark CAR-BOPOL® 934 from B. F. Goodrich Chemical Co., which is said to form a high viscosity gel-like dispersion in water.

U.S. Patent No. 4,548,990 discloses a controlled-release drug delivery composition whose cross-linked polymeric portion is prepared from monomers that include 50 to 99 percent of a water-insoluble monoolefinic monomer or mixture. The polymer is said to swell in ethanol and in water with a swelling ratio of 2:1 to 22:1.

Candida also causes vulvovaginitis, meningitis, pulmonary candidiasis, thrush, and endocarditis. It is most often associated, however, with the organism that is responsible for vaginal yeast infections in women. This condition occurs most frequently, and with greater severity, in areas where the climate is warm and moist. It often follows antibiotic therapy and is difficult to eradicate.

Conventional commercially-available treatments for vaginal yeast infections are creams which cause leakage and suffer serious negatives in terms of skinfeel (i.e. they often feel very tacky and greasy on the skin). They also have poor absorption and residue characteristics.

The present invention provides topical moisturizing compositions in the form of an aqueous gel which treat microbial infections which provide improvements in residue and skinfeel characteristics.

It is therefore an object of the present invention to provide improved compositions which are excellent carriers for certain antimicrobial actives and which provide reduced tack and provide the user with an improved skinfeel.

SUMMARY OF THE INVENTION

The present invention relates to pharmaceutical compositions for moisturizing membranous tissue and treating infections comprising:

- (a) a safe and effective amount of an antimicrobial;
 - (b) a moisturizing component; and
 - (c) an pharmaceutically acceptable aqueous gel carrier
- wherein said composition has a viscosity of from about 40,000 cps to about 100,000 cps.

The present invention also relates to a method for treatment of dry membranous tissue and treating infections comprising administering a safe and effective amount of these topical compositions and to methods for the prophylactic treatment of infection by application of these compositions to healthy membranous tissue.

All levels and ratios are by weight of the total composition, unless otherwise indicated.

DETAILED DESCRIPTION OF THE INVENTION

The compositions of the present invention contain the essential components as well as various optional components as indicated below.

Humectants/Moisturizers. The compositions of the instant invention comprise one or more water-soluble humectants/moisturizers. A variety of humectants/moisturizers can be employed and can be present at a level of from about 1% to about 10%, more preferably from about 2% to about 8% and most preferably from about 3% to about 5%. These materials include the C₃-C₆ diols and triols; urea; guanidine; glycolic acid and glycolate salts (e.g. ammonium and quaternary alkyl ammonium); lactic acid and lactate salts (e.g. ammonium and quaternary alkyl ammonium); polyhydroxy alcohols such as sorbitol, glycerin, hexanetriol, propylene glycol, hexylene glycol and the like; polyethylene glycol; sugars and starches; sugar and starch derivatives (e.g. alkoxylated glucose); D-panthenol; hyaluronic acid; lactamide monoethanolamine; acetamide monoethanolamine; and mixtures thereof.

Preferred humectants/moisturizers for use in the compositions of the present invention are the C₃-C₆ diols and triols. Especially preferred is the triol, glycerin.

Antimicrobial Agent

The antimicrobial agents useful in the present invention can be present at a level of from about 0.01% to about 4%, typically from about 0.1% to about 2%, and preferably from about 0.5% to about 1%. The level is selected to provide the desired level of antimicrobial activity and can be modified as desired.

Useful antimicrobial agents include those effective against microsporum audouini, microsporum gypseum, microsporum gypseum-canis, epidermophyton floccosum, trichophyton mentagrophytes, trichophyton rubrum, trichophyton tonsurans, cryptococcus neoformans and the candida species, including candida albicans and candida tropicalis.

In addition, the compounds of the present invention exhibit antimicrobial activity against human and animal pathogens, such as staphylococcus aureus, streptococcus faecalis, corynebacterium acnes, erysipelothrix insidiosa, escherichia coli, proteus vulgaris, salmonella choleraesuis, pasteurilla multocida, pseudomonas aeruginosa and trichomonas vaginalis.

Many antimicrobial agents, known to those skilled in the art and disclosed in, e.g., U.S. Pat. Nos. 3,835,057 and 4,714,563, both incorporated herein by reference, may be used.

Suitable antimicrobial agents include: 2-hydroxy-4,2',4'-trichlorodiphenylether,

(TCS); 2,6-dimethyl-4-hydroxychlorobenzene (PCMX); 3,4,4'-trichlorocarbanilide (TCC); 3-trifluoromethyl-4,4'-dichlorocarbanilide (TFC); 2,2'-dihydroxy-3,3',5,5',6,6'-hexachlorodiphenylmethane; 2,2'-dihydroxy-3,3',5,5'-tetrachlorodiphenylmethane; 2,2'-dihydroxy-3,3',dibromo-5,5'-dichlorodiphenylmethane; 2-hydroxy-4,4'-dichlorodiphenylether; 2-hydroxy-3,5',4-tribromodiphenylether; 1-hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2(1H)-pyridinone (Octopirox); butoconazole, nystatin, terconazole, nitrofurantoin, phenazopyridine, acyclovir, clotrimazole, chlorohexidine, terconazole and miconazole. The most preferred antimicrobials of this group are butoconazole, nystatin, terconazole, nitrofurantoin, phenazopyridine, acyclovir, chlorohexidine, miconazole, and clotrimazole.

Also preferred for use herein are the 1-(β -aryl) ethyl-imidazole ethers and amines disclosed in U.S. Patent 3,717,655 to Godefroi et al. issued February 20, 1973 derivatives of substituted N-alkyl imidazoles disclosed in U.S. Patent 4,078,071 to Walker, issued March 7, 1978. Other preferred antimicrobials include the tin-containing polymers disclosed in U.S. Patent 5,043,463 to Carraher Jr., et al., issued August 27, 1991. All of these patents are incorporated by reference herein.

Pharmaceutical Carrier

The pharmaceutical compositions of the present invention may be made into a wide variety of product types having a pharmaceutically-acceptable aqueous-based gel-type carriers. Such gel carriers contain a hydrophilic gelling agent at a level preferably from about 0.05% to about 1%, more preferably from about 0.1% to about 1%. The gelling agent preferably has a viscosity (1% aqueous solution, 20°C, Brookfield RVT) of at least about 4000 cps, more preferably at least about 10,000 cps, and most preferably at least about 50,000.

Suitable hydrophilic gelling agents can generally be described as water-soluble or colloiddally water-soluble polymers, and include cellulose ethers (e.g. hydroxyethyl cellulose, methyl cellulose), hydroxypropyl guar gum and xanthan gum. Also useful are clays such as hectorite (Veegum) and bentonite. Particularly preferred gelling agents useful in the present invention are polyacrylamides and substituted polyacrylamides, branched or unbranched. These polymers are non-ionic water-dispersible polymers which can be formed from a variety of monomers including acrylamide and methacrylamide which are unsubstituted or substituted with one or two alkyl groups (preferably C₁-C₅). Preferred acrylate amides and methacrylate amides in which the amide nitrogen is unsubstituted, or substituted with one or two C₁-C₅ alkyl groups (preferably: methyl, ethyl or propyl), for example, acrylamide, methacrylamide, N-methylacrylamide, N-methylmethacrylamide, N,N-dimethylmethacrylamide, N-isopropylacrylamide, N-isopropylmethacrylamide and N,N-dimethylacrylamide. These

monomers are generally disclosed in U. S. Patent 4,963,348 to Bolich, Jr. et al., issued October 16, 1990, incorporated by reference herein in its entirety. These copolymers may optionally be formed using conventional neutral crosslinking agents such as dialkenyl compounds. The use of such crosslinking agents for cationic polymers is disclosed in U.S. Patent 4,628,078 to Glover et al. issued December 9, 1986 and U.S. Patent 4,599,379 to Flesher et al. issued July 8, 1986 both of which are incorporated by reference herein. These non-ionic copolymers have a molecular weight greater than about 1,000,000 preferably greater than about 1,500,000 and range up to about 30,000,000. Preferably these non-ionic polyacrylamides are pre-dispersed in a water-immiscible solvent such as mineral oil and the like, containing a high HLB surfactant (HLB from about 7 to about 10) which helps to facilitate water dispersibility of the polyacrylamide. Most preferred for use herein is the non-ionic polymer under the CTFA designation: polyacrylamide and isoparaffin and laureth-7, available as Sepigel from Seppic Corporation.

In highly preferred embodiment, the compositions are substantially free of materials which are insoluble or not colloiddally soluble in distilled water at 20°C. Such materials include many conventional emollient materials such as hydrocarbon oils and waxes, fatty alcohols, certain fatty alcohol ethers and sterols extracted from lanolin, beeswax derivatives, vegetable waxes, sterols and amides. The compositions can, however, contain low levels of insoluble ingredients added, for example for visual effect purposes, e.g., titanium mica.

These compositions may include additional co-solvents such as ethanol, isopropanol, butylene glycol, hexylene glycol, polyethylene glycol and polypropylene glycol.

The compositions of the invention have no need of additional surfactant materials which are conventionally added to cosmetic cream and lotion compositions in order to emulsify a water-insoluble oily phase.

The pharmaceutical compositions of the present invention typically include a pharmaceutically or cosmetically-acceptable organic solvent. The terms "pharmaceutically-acceptable organic solvent" and "cosmetically-acceptable organic solvent" refer to an organic solvent which also possesses acceptable safety (e.g. irritation and sensitization characteristics), as well as good aesthetic properties (e.g., does not feel greasy or tacky). The most typical example of such a solvent is water. Examples of other suitable organic solvents include: propylene glycol, polyethylene glycol (200-600), polypropylene glycol (425-2025), glycerol, 1,2,4-butanetriol, sorbitol esters, 1,2,6-hexanetriol, ethanol, isopropanol, butanediol, and mixtures thereof.

The compositions of the invention are formulated so as to have product vis-

cosity in the range of from about 40,000 to about 100,000 cps, more preferably from about 40,000 to about 80,000 cps and especially from about 40,000 to about 60,000 cps (20°C, neat, Brookfield RVT). Preferably the compositions are visually translucent.

5 The compositions which are in aqueous form are also preferably substantially free of oil, i.e. contain less than about 1%, and preferably less than about 0.1% of materials which are insoluble or which are not colloiddally-soluble in the aqueous gel matrix at 10°C. "Colloiddally-soluble" herein refers to particles in the usual colloiddal size range, typically from 1 to 1000 nm, especially from 1 to 500 nm. In highly preferred embodiment, the compositions are substantially free of materials which are insoluble or not colloiddally soluble in distilled water at 20°C. Such materials include many conventional emollient materials such as hydrocarbon oils and waxes, fatty alcohols, certain fatty alcohol ethers and sterols extracted from lanolin, beeswax derivatives, vegetable waxes, sterols and amides. The compositions are also preferably 10 substantially free of alcohol, i.e. contain less than about 5%, preferably less than about 0.3%, more preferably less than about 1% and most preferably less than about 0.5% alcohol. The compositions can, however, contain low levels of insoluble ingredients added, for example for visual effect purposes, e.g., titanated mica.

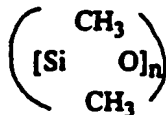
20 These compositions can be delivered from, for example, applicators, dispensers, wipes or towelettes (including baby wipes and the like) or also incorporated into feminine hygiene products such as sanitary napkins and the like.

Optional Components

Emollients. The compositions of the present invention preferably comprise at least one emollient. Useful emollients have a required HLB below about 10. Preferred emollients are volatile silicone oils, non-volatile emollients, and the highly 25 branched hydrocarbons known as the Permethyl 99 through 108A series (available from Permethyl Corporation) and mixtures thereof. The compositions of the present invention more preferably comprise at least one volatile silicone oil which functions as a liquid emollient, or especially in a mixture of volatile silicone oils and non-volatile emollients. The term "volatile", as used herein, refers to those materials which 30 have a measurable vapor pressure at ambient temperature.

Volatile silicone oils useful in the compositions of the present invention are preferably cyclic. The following formula illustrates cyclic volatile polydimethylsiloxanes useful in the compositions disclosed herein:

35



wherein n equals about 3 to about 7. Linear polydimethylsiloxanes contain from about 3 to about 9 silicon atoms per molecule and have the following general formula:



- 5 wherein n equals about 1 to about 7. Linear volatile silicone materials generally have viscosities of less than about 5 centistokes at 25°C while cyclic materials typically have viscosities of less than about 10 centistokes. A description of various volatile silicone oils is found in Todd, et al., "Volatile Silicone Fluids for Cosmetics", Cosmetics & Toiletries, 91, pages 27-32 (1976), the disclosures of which are incorporated by reference herein in their entirety.

10 Examples of preferred volatile silicone oils useful herein include: Dow Corning 344, Dow Corning 345, and Dow Corning 200 (manufactured by Dow Corning Corp.); Silicone 7207 and Silicone 7158 (manufactured by the Union Carbide Corp.); SF 1202 (manufactured by General Electric); and SWS-03314 (manufactured by
15 SWS Silicones, Inc.).

The present compositions also preferably contain one or more non-volatile emollients. Such materials include fatty acid and fatty alcohol esters, hydrocarbons, non-volatile silicone oils, and mixtures thereof. Emollients among those useful herein are described in 1 Cosmetics, Science and Technology 27-104 (M. Balsam and E. Sagarin, Ed.; 1972), and U.S. Patent 4,202,879, to Shelton, issued May 13, 1980
20 (both incorporated by reference herein).

Non-volatile silicone oils useful as an emollient material include polyalkylsiloxanes and polyalkylarylsiloxanes. The essentially non-volatile polyalkyl siloxanes useful herein include, for example, polydimethyl siloxanes with viscosities of from about
25 5 to about 100,000 centistokes at 25°C. Among the preferred non-volatile emollients useful in the present compositions are the polydimethyl siloxanes having viscosities from about 10 to about 400 centistokes at 25°C. Such polyalkyl siloxanes include the Vicasil series (sold by General Electric Company) and the Dow Corning 200 series (sold by Dow Corning Corporation). Polyalkylaryl siloxanes include poly
30 methylphenyl siloxanes having viscosities of from about 15 to about 65 centistokes at 25°C. These are available, for example, as SF 1075 methylphenyl fluid (sold by General Electric Company) and 556 Cosmetic Grade Fluid (sold by Dow Corning Corporation).

Non-polar fatty acid and fatty alcohol esters useful herein as an emollient material include, for example, ethyl hexyl palmitate, isodecyl neopentanoate, octadecyl benzoate, diethyl hexyl maleate and PPG-2 myristyl ether propionate. Hydro-
35

carbons such as isohexadecane (e.g., Permethyl 101A supplied by Presperse), petrolatum and USP light (e.g. Klearol®) or heavy (e.g. Kaydol®) mineral oils are also useful as emollients. Emollients useful in the instant invention are further described in U.S. Patent No. 4,919,934, to Deckner et al., issued April 24 1990, which is incorporated herein by reference in its entirety.

The emollients typically comprise in total from about 1% to about 50%, preferably from about 1% to about 25%, and more preferably from about 1% to about 10% by weight of the compositions of the present invention.

Thickening Agents. The composition may also comprise from about 0.1% to about 2% of a thickening agent. Examples of suitable thickening agents include: cellulose derivatives (e.g., methyl cellulose and hydroxy propylmethyl cellulose), synthetic high molecular weight polymers (e.g., carboxyvinyl polymer and polyvinyl alcohol), plant hydrocolloids (e.g., karaya gum and tragacanth gum), clay thickeners (e.g., colloidal magnesium aluminum silicate and bentonite), and carboxyvinyl polymers are described in detail in U.S. Patent 2,798,053, Brown, issued July 2, 1975, incorporated herein by reference). A more complete disclosure of thickening agent useful herein can be found in Segarin, Cosmetics, Science and Technology, 2nd Edition, Vol. 1, pp. 72-73 (1972), incorporated herein by reference.

Additional Pharmaceutical Actives. Optional pharmaceutical actives useful in the present invention include any chemical material or compound suitable for topical administration; however, such drugs should be included so as not to interfere with the stability of the composition. These actives are present at a level from about 0.1% to about 20%. Such substances include, but are not limited to vitamins, analgesics, anti-inflammatory agents, antipuritics, antipyretics, anesthetic agents, and mixtures thereof.

A safe and effective amount of an anti-inflammatory agent may be added to the compositions of the present invention, preferably from about 0.1% to about 10%, more preferably from about 0.5% to about 5%, of the composition. The exact amount of anti-inflammatory agent to be used in the compositions will depend on the particular anti-inflammatory agent utilized since such agents vary widely in potency.

Steroidal anti-inflammatory agents, including but not limited to, corticosteroids such as hydrocortisone, hydroxyltriamcinolone, alpha-methyl dexamethasone, dexamethasone-phosphate, beclomethasone dipropionate, clobetasol valerate, desonide, desoxymethasone, desoxycorticosterone acetate, dexamethasone, dichlorisone, diflorasone diacetate, difluocortolone valerate, fluadrenolone, fluclorolone acetonide, fludrocortisone, flumethasone pivalate, fluosinolone acetonide, fluocinonide, flucortine butylester, fluocortolone, fluprednidene (fluprednylidene) acetate, flurandre-

nolone, halcinonide, hydrocortisone acetate, hydrocortisone butyrate, methylprednisolone, triamcinolone acetonide, cortisone, cortodoxone, flucetonide, fludrocortisone, difluorosone diacetate, fluradrenolone acetonide, medrysone, amcinafel, amcinafide, betamethasone and the balance of its esters, chloroprednisone, chlorprednisone acetate, clocortelone, clescincolone, dichlorisone, difluprednate, flucoronide, flunisolide, fluoromethalone, fluperolone, fluprednisolone, hydrocortisone valerate, hydrocortisone cyclopentylpropionate, hydrocortamate, meprednisone, paramethasone, prednisolone, prednisone, beclomethasone dipropionate, triamcinolone, and mixtures thereof may be used. The preferred steroidal anti-inflammatory for use in the present invention is hydrocortisone.

A second class of anti-inflammatory agents which is useful in the compositions of the present invention includes the nonsteroidal anti-inflammatory agents. The variety of compounds encompassed by this group are well-known to those skilled in the art. For detailed disclosure of the chemical structure, synthesis, side effects, etc., of non-steroidal anti-inflammatory agents, reference may be had to standard texts, including Anti-inflammatory and Anti-Rheumatic Drugs, K. D. Rainsford, Vol. I-III, CRC Press, Boca Raton, (1985), and Anti-inflammatory Agents, Chemistry and Pharmacology, 1, R. A. Scherrer, et al., Academic Press, New York (1974).

Specific non-steroidal anti-inflammatory agents useful in the composition of the present invention include, but are not limited to:

- 1) the oxicams, such as piroxicam, isoxicam, tenoxicam, sudoxicam, and CP-14,304;
- 2) the salicylates, such as aspirin, disalcid, benorylate, trilisate, safapryn, solprin, diflunisal, and fendosal;
- 3) the acetic acid derivatives, such as diclofenac, fenclofenac, indomethacin, sulindac, tolmetin, isoxepac, furofenac, tiopinac, zidometacin, acematacin, fentiazac, zomepiract, clidanac, oxepinac, and felbinac;
- 4) the fenamates, such as mefenamic, meclofenamic, flufenamic, niflumic, and tolfenamic acids;
- 5) the propionic acid derivatives, such as ibuprofen, naproxen, benoxaprofen, flurbiprofen, ketoprofen, fenoprofen, fenbufen, indoprofen, piroprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, and tiaprofenic; and
- 6) the pyrazoles, such as phenybutazone, oxyphenbutazone, feprazone, azapropazone, and trimethazone.

Mixtures of these non-steroidal anti-inflammatory agents may also be employed, as well as the pharmaceutically-acceptable salts and esters of these agents. For exam-

ple, etofenamate, a flufenamic acid derivative, is particularly useful for topical application. Of the nonsteroidal anti-inflammatory agents, ibuprofen, naproxen, flufenamic acid, mefenamic acid, meclofenamic acid, piroxicam and felbinac are preferred; ibuprofen, naproxen, and flufenamic acid are most preferred.

5 Another class of anti-inflammatory agents which are useful in the present invention are the anti-inflammatory agents disclosed in U.S. Patent No. 4,708,966, Loomans et al., issued November 24, 1987. This patent discloses a class of nonsteroidal anti-inflammatory compounds which comprise specifically substituted phenyl compounds, especially substituted 2,6-di-tert-butyl phenol derivatives. For example,
10 compounds selected from 4-(4'-pentyn-3'-one)-2,6-di-*t*-butylphenol; 4-(5'-hexynoyl)-2,6-di-*t*-butylphenol; 4-((S)-(-)-3'-methyl-5'-hexynoyl)-2,6-di-*t*-butylphenol; 4-((R)-(+)-3'-methyl-5'-hexynoyl)-2,6-di-*t*-butylphenol; and 4-(3',3'-dimethoxypropionyl)-2,6-di-*t*-butylphenol are useful in the present invention.

15 Yet another class of anti-inflammatory agents which are useful in the present invention are those disclosed in U.S. Patent No. 4,912,248, Mueller, issued March 27, 1990. This patent discloses compounds and diastereomeric mixtures of specific 2-naphthyl- containing ester compounds, especially naproxen ester and naproxol ester compounds, having two or more chiral centers.

20 Finally, so-called "natural" anti-inflammatory agents are useful in the present invention. For example, candelilla wax, alpha bisabolol, aloe vera, Manjistha (extracted from plants in the genus Rubia, particularly Rubia Cordifolia), and Guggal (extracted from plants in the genus Commiphora, particularly Commiphora Mukul), may be used.

25 Useful anesthetic or antipruritic drugs are selected from the group consisting of lidocaine, lidocaine hydrochloride, bupivacaine hydrochloride, chlorprocaine hydrochloride, dibucaine hydrochloride, etidocaine hydrochloride, mepivacaine hydrochloride, tetracaine, tetracaine hydrochloride, dyclonine hydrochloride and hexylcaine hydrochloride, benzocaine, benzyl alcohol, butamben picrate, camphor, camphorated metacresol, dibucaine, dibucaine hydrochloride, dimethisoquin hydrochloride,
30 diphenhydramine hydrochloride, juniper tar, menthol, phenol, phenolate sodium, pramoxine hydrochloride, resorcinol and mixtures thereof.

35 Other Optional Components. A variety of additional ingredients may be added to the emulsion compositions of the present invention. These additional ingredients include various polymers for aiding the film-forming properties and substantivity of the formulation, preservatives for maintaining the antimicrobial integrity of the compositions, antioxidants, and agents suitable for aesthetic purposes such as fragrances, pigments, and colorings.

The compositions can also contain low levels of insoluble ingredients added, for example for visual effect purposes, e.g. thermochromic liquid crystalline materials such as the microencapsulated cholesteryl esters and chiral nematic (nonsterol) based chemicals such as the (2-methylbutyl) phenyl 4-alkyl(oxy)benzoates available from
5 Hallcrest, Glenview, Illinois 60025, U.S.A.

Also preferred for use herein is a bioadhesive which will adhere the microbial agent of the present invention to the skin tissues treated herein. Useful bioadhesives are described in U.S. Patent 4,983,392 to Robinson et al., incorporated by reference herein.

10 The pH of the compositions is preferably from about 3 to about 8, more preferably from about 3 to about 7.

The amount of active components and frequency of treatment will vary widely depending upon the individual.

For treatment, the composition is applied to the mucosal skin via topical application of a safe and effective amount of the composition to treat an existing fungal, microbial or protozoal growth. Preferably, the compositions of the present invention are used to treat vaginal yeast infections. The amount of actives and frequency of topical application to the skin can vary widely, depending upon personal needs, but it is suggested as an example that topical application range from about once per day to
15 about four times daily, preferably from about twice per day to about three times daily. The amount of antifungal agents applied is generally from about 1 mg to about 2 mg per cm² skin. The compositions of the present invention can also be used prophylactically by their administration to healthy membranous tissues to guard from or prevent infections using the dosing regimen described above.

25 For vaginal use, the compositions of the present invention can also be applied via applicator such as from any of those disclosed in U.S. Patent 3,050,217 to Mackey issued August 21, 1962, U.S. Patent 4,636,202 to Lowin et al. issued January 13, 1987 and in U.S. Patent 4,200,097 to Hobbs, Jr. et al. issued April 29, 1980 both of which are incorporated by reference herein.

30 EXAMPLES

The following examples further describe and demonstrate embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention, as many variations thereof are possible without departing from the spirit and scope of
35 the invention.

Ingredients are identified by chemical or CTFA name.

Example I

An antimicrobial composition is made by combining the following components using conventional mixing technology.

| | <u>Ingredient</u> | <u>(%W/W)</u> |
|---|--|---------------|
| 5 | Polyacrylamide and C ₁₃₋₁₄ | |
| | Isoparaffin and Laureth-7 ¹ | 4.0 |
| | Clotrimazole | 2.0 |
| | PPG-14 Butylether | 8.0 |
| | Water, Purified | q.s. |

10 ¹ Available as Sepigel from Seppic Corporation.

Water is added to a suitable size container. While mixing at a moderate speed (300 rpm), the Polyacrylamide and C₁₃₋₁₄ Isoparaffin and Laureth-7 is added to the water. Separately, the PPG-14 Butyl ether is placed in a container and covered. Using a Lightnin' Mixer with a 3 blade paddle prop, the clotrimazole is added to the PPG-14 Butyl ether and mixed at a low speed (100 rpm) until the clotrimazole is dissolved. The PPG-14 Butyl ether is slowly added to the water phase to form a gel. The resulting gel is mixed at moderate speed until uniform.

The compositions display improved skinfeel and residue characteristics together with excellent moisturizing and emolliency characteristics.

20

Example II

An antimicrobial composition is made by combining the following ingredients utilizing conventional mixing techniques as described above in Example I.

| | <u>Ingredient</u> | <u>(%W/W)</u> |
|----|---------------------------------------|---------------|
| | Polyacrylamide and C ₁₃₋₁₄ | |
| 25 | Isoparaffin and Laureth-7 | 4.0 |
| | benzocaine | 3.0 |
| | clotrimazole | 2.0 |
| | PPG-14 butyl ether | 8.0 |
| | Water, Purified | q.s. |

30

An antimicrobial composition is made by combining the following ingredients utilizing conventional mixing techniques as described above in Example I.

Example III

| | <u>Ingredient</u> | <u>(%W/W)</u> |
|----|---------------------------------------|---------------|
| | PPG-14 butyl ether | 8.000 |
| 35 | Polyacrylamide and C ₁₃₋₁₄ | |
| | Isoparaffin and Laureth-7 | 4.000 |
| | clotrimazole | 2.000 |

| | | |
|---|-----------------|-------|
| | Ibuprofen | 5.000 |
| | Glycerin | 1.000 |
| | Aloe Vera Gel | 0.500 |
| | Disodium EDTA | 0.005 |
| 5 | Water, Purified | q.s. |

- The PPG-14 Butyl ether is added to a suitable size container. Using a Lightnin' mixer with a 3 blade paddle prop, the ibuprofen and clotrimazole are added to the PPG-14 Butyl ether and mixed at low speed (100 rpm) until the ibuprofen is dissolved. Menthol is added to the PPG-14 Butyl ether and mixed until dissolved.
- 10 Separately, water is added to a suitable size container. Aloe vera gel and disodium EDTA are added to the water and mixed at low speed (100 rpm) until completely dissolved. The water phase is then added to the PPG-14 Butyl ether phase and mixed until clear. Glycerin is added and mixed until clear. While mixing at moderate speed (300 rpm), the polyacrylamide and C₁₃₋₁₄ isoparaffin and laureth-7 is added to
- 15 form a gel. The resulting gel is mixed at moderate speed until uniform.

What is Claimed is:

1. A pharmaceutical composition for moisturizing membranous tissue and treating infections comprising:
 - (a) a safe and effective amount of an antimicrobial;
 - (b) a moisturizing component; and
 - (c) an pharmaceutically-acceptable aqueous gel carrierwherein said composition has a viscosity of from 40,000 to 100,000 cps (20°C, neat, Brookfield RVT).
2. A pharmaceutical composition according to Claim 1 wherein said moisturizing component is selected from the group consisting of the C₃-C₆ diols and triols, urea, guanidine, glycolic acid, glycolate salts, lactic acid, polyhydroxy alcohols, polyethylene glycol, sugar derivatives, starch derivatives, D-panthenol, hyaluronic acid, lactamide monoethanolamine, acetamide monoethanolamine, derivatives thereof and mixtures thereof, preferably wherein said moisturizing component is selected from the group consisting of the C₃-C₆ diols and triols; sorbitol; glycerin; hexanetriol, propylene glycol, hexylene glycol derivatives thereof and mixtures thereof.
3. A pharmaceutical composition according to Claim 2 wherein said antimicrobial is selected from the group consisting of 2-hydroxy-4,2',4'-trichlorodiphenylether, (TCS); 2,6-dimethyl-4-hydroxychlorobenzene (PCMX); 3,4,4'-trichlorocarbanilide (TCC); 3-trifluoromethyl-4,4'-dichlorocarbanilide (TFC); 2,2'-dihydroxy-3,3',5,5',6,6'-hexachlorodiphenylmethane; 2,2'-dihydroxy-3,3',5,5'-tetrachlorodiphenylmethane; 2,2'-dihydroxy-3,3',dibromo-5,5'-dichlorodiphenylmethane; 2-hydroxy-4,4'-dichlorodiphenylether; 2-hydroxy-3,5',4-tribromodiphenylether; 1-hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2(1H)-pyridinone (Octopirox); butoconazole, nystatin, terconazole, nitrofurantoin, phenazopyridine, acyclovir, clotrimazole, 1-(β-aryl) ethyl-imidazole ethers and amines, derivatives thereof and mixtures thereof.
4. A pharmaceutical composition according to any of the preceding Claims wherein said gelling agent is non-ionic polyacrylamide having a molecular weight of from 1,000,000 to 30,000,000 and has a viscosity of from 40,000 to 80,000 cps.
5. A pharmaceutical composition according to any of the preceding Claims wherein said polyacrylamide comprises monomers selected from acrylamide and

methacrylamide which are unsubstituted or substituted with at least one alkyl groups having from 1 to 5 carbon atoms.

6. A pharmaceutical composition according to any of the preceding Claims wherein said composition further comprises an additional pharmaceutical active, preferably said additional pharmaceutical active is selected from the group consisting of vitamins, analgesics, anti-inflammatory agents, antipuritics, antipyretics, anesthetic agents, and mixtures thereof.

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | |
|---|-----------|---|
| (51) International Patent Classification ⁶ : A61K 9/00 | A3 | (11) International Publication Number: WO 95/17165 (43) International Publication Date: 29 June 1995 (29.06.95) |
| (21) International Application Number: PCT/US94/14756 (22) International Filing Date: 21 December 1994 (21.12.94) (30) Priority Data: 08/172,451 23 December 1993 (23.12.93) US (71) Applicant: THE PROCTER & GAMBLE COMPANY [US/US]; One Procter & Gamble Plaza, Cincinnati, OH 45202 (US). (72) Inventors: MITRA, Sekhar , 7305 Demar Road, Cincinnati, OH 45243 (US). DECKNER, George, Endel ; 10572 Tanager Hills Drive, Cincinnati, OH 45209 (US). (74) Agents: REED, T., David et al. ; The Procter & Gamble Company, 5299 Spring Grove Avenue, Cincinnati, OH 45217 (US). | | (81) Designated States: CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 20 July 1995 (20.07.95) |
| (54) Title: TISSUE MOISTURIZING AND ANTIMICROBIAL COMPOSITIONS (57) Abstract The present invention relates to improved topical pharmaceutical compositions having improved aesthetics which are useful for imparting antimicrobial active. In particular, it relates to topical moisturizing compositions containing one or more antimicrobial active compounds. These compositions are also useful for providing relief from symptoms associated with, for example, vaginal yeast infections. | | |

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | |
|----|--------------------------|----|---------------------------------------|----|--------------------------|
| AT | Austria | GB | United Kingdom | MR | Mauritania |
| AU | Australia | GE | Georgia | MW | Malawi |
| BB | Barbados | GN | Guinea | NE | Niger |
| BE | Belgium | GR | Greece | NL | Netherlands |
| BF | Burkina Faso | HU | Hungary | NO | Norway |
| BG | Bulgaria | IE | Ireland | NZ | New Zealand |
| BJ | Benin | IT | Italy | PL | Poland |
| BR | Brazil | JP | Japan | PT | Portugal |
| BY | Belarus | KE | Kenya | RO | Romania |
| CA | Canada | KG | Kyrgyzstan | RU | Russian Federation |
| CF | Central African Republic | KP | Democratic People's Republic of Korea | SD | Sudan |
| CG | Congo | KR | Republic of Korea | SE | Sweden |
| CH | Switzerland | KZ | Kazakhstan | SI | Slovenia |
| CI | Côte d'Ivoire | LI | Liechtenstein | SK | Slovakia |
| CM | Cameroon | LK | Sri Lanka | SN | Senegal |
| CN | China | LU | Luxembourg | TD | Chad |
| CS | Czechoslovakia | LV | Latvia | TG | Togo |
| CZ | Czech Republic | MC | Monaco | TJ | Tajikistan |
| DE | Germany | MD | Republic of Moldova | TT | Trinidad and Tobago |
| DK | Denmark | MG | Madagascar | UA | Ukraine |
| ES | Spain | ML | Mali | US | United States of America |
| FI | Finland | MN | Mongolia | UZ | Uzbekistan |
| FR | France | | | VN | Viet Nam |
| GA | Gabon | | | | |

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 94/14756

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X | US-A-5 244 666 (MURLEY) 14 September 1993 see the whole document | 1 |
| X | EP-A-0 524 602 (BRISTOL-MEYERS SQUIBB CO) 27 January 1993 see the whole document | 1,6 |
| X | US-A-5 219 877 (SHAH ET AL.) 15 June 1993 see the whole document | 1,6 |
| A | US-A-4 956 170 (LEE) 11 September 1990 | |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- 'A' document defining the general state of the art which is not considered to be of particular relevance
- 'E' earlier document but published on or after the international filing date
- 'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- 'O' document referring to an oral disclosure, use, exhibition or other means
- 'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search

8 June 1995

Date of mailing of the international search report

21.06.95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Klaver, T

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter. Natl Application No

PCT/US 94/14756

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|--|--|
| US-A-5244666 | 14-09-93 | NONE | |
| EP-A-524602 | 27-01-93 | US-A- 5208015 AU-A- 2046792 JP-A- 5194219 ZA-A- 9205288 | 04-05-93 28-01-93 03-08-93 02-04-93 |
| US-A-5219877 | 15-06-93 | NONE | |
| US-A-4956170 | 11-09-90 | AU-A- 5945990 WO-A- 9100087 | 17-01-91 10-01-91 |